SOME RULES FOR DOSAGE OF PROTAMINE ZINC INSULIN

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After two years' experience in the use of protamine zinc insulin we are beginning to know the benefits and difficulties in its administration. We were thankful, at first, to have an insulin whose effects would last all night. It is a great blessing to those severe diabetics who had to set the alarm and rise at 2 o'clock in the morning to take one night dose of insulin; soon we found that the effect lasted all night and all day, and, probably, the next night. Then we began giving one dose in the twenty-four hours before breakfast, in some cases an hour before breakfast, but after getting some severe reactions while waiting for breakfast we now give it immediately before breakfast. At the present time its use is fairly well standardized, which it must be if it is in general use by physicians who treat only an occasional diabetic.

This paper presents some simple rules in the administration of protamine zinc insulin which the general practitioner can apply.

The amount of blood sugar at any given time is the result of three factors—food, insulin and exercise. Possibly temperature is also a factor. In the first warm days in May reactions seem more plentiful than in the cold weather or in the very hot summer, but this may be because it is a pleasure to take more exercise. The effect of insulin administration seems to be more predictable than the effect of food ingestion or of exercise indulged in.

Night blood sugars were studied on two diabetics, one was taking unmodified insulin, the other was not taking any. Blood sugars were taken every hour from 8 p.m. to 5 a.m. on the insulin case and every hour up till 3 a.m. on the non-insulin case. Results are seen in Table I. The blood sugar of the patient who was not taking insulin was high after food but steadily fell until midnight, when it became stationary for three hours; a slight rise occurred at 3 a.m., but an average fall of 10.5 mg. per hour occurred between 8 p.m. and 2 a.m. In the insulin case a low point was reached approximately four hours after insulin was given. No evening food was given. The blood sugar rose from 39 mg. per

TABLE I.

BLOOD SUGAR MG. PER 100 C.C.

Time	*Case 1 Mrs. C (no insulin)*	*Case 2—Mrs. F. 20 units at 4.40 p.m. supper at 5*
8 p.m	223	53
9 p.m.	216	39
10 p.m.	209	46
11 p.m.	223	81
12 m.n.	160	88
1 a.m.	160	95
2 a.m.	160	109
3 a.m.	174	109
4 a.m.	–	123
5 a.m.	–	153
6 a.m.	–	–
8 a.m.	–	174

Case 1.—An average fall of 10.5 mg. per hour for 6 hours.

Case 2.—A rise of 12 mg. per hour from 9 p.m. to 8 a.m.

TABLE II.

Case 1—Jack P.

Date	*Time*	*Blood sugar*	*Insulin*
23-10-37	8 a.m.	–	55 p.z.i.
	11 a.m.	141	–
	2 p.m.	160	–
	5 p.m.	250	–
	10 p.m.	136	–
24-10-37	7 a.m.	59	–

Rate of fall 8.5 mg. per hour.

Case 2—Murdock M.

Date	*Time*	*Blood sugar*	*Insulin*
30-4-37	8 a.m.	70	–
	8.15 a.m.	–	120 p.z.i.
	10 p.m.	127	–
1-5-37	8 a.m.	73	–

Rate of fall 5.4 mg. per hour.

Case 3—Christine H.

Date	*Time*	*Blood sugar*	*Insulin*
4-9-37	8 a.m.	–	45 p.z.i.
	10 p.m.	169	–
5-9-37	1 a.m.	98	–
	6 a.m.	48	–

Rate of fall 15.1 mg. per hour.
Sugar present in urine from 1 p.m. to 9.30 p.m.

Case 4—Gordon L.

Date	*Time*	*Blood sugar*	*Insulin*
9-12-37	8 a.m.	–	30 p.z.i.
	10 p.m.	198	–
10-12-37	6 a.m.	60	30 p.z.i.

Rate of fall 17.2 mg. per hour.

Case 5—William C.

Date	*Time*	*Blood sugar*	*Insulin*
18-5-37	8 a.m.	–	18 p.z.i.
	10 p.m.	119	–
19-5-37	7 a.m.	89	–
	8 a.m.	–	18 p.z.i.
	11 a.m.	265	–

Rate of fall 3.3 mg. per hour.
Patient showed sugar all day.

Case 6—Phyllis H.

Date	*Time*	*Blood sugar*	*Insulin*
19-12-37	8 a.m.	–	50 p. 10 u.
	10 p.m.	124	–
20-12-37	6 a.m.	92	–
	8 a.m.	–	40 p. 10 u.
	10 p.m.	166	–
21-12-37	6 a.m.	96	–

Rate of fall first night 4 mg. per hour.
Rate of fall second night 8.7 mg. per hour.

cent to 174 mg. per cent at 8 a.m., an average rise of 12 mg. per hour. Some people find it hard to understand why a patient could have symptoms of hypoglycæmia at 10 p.m. and without ingestion of food show sugar before breakfast. This tendency of the night blood sugar to rise in severe diabetes explains why insulin had to be given at 2 a.m.

With the administration of protamine zinc insulin the night blood sugar pattern was again changed; after the evening meal had been absorbed the blood sugar continued to fall all night, see Table II. We make use of the rate of this night blood sugar fall in deciding the suitable dose of protamine zinc insulin for the patient. We have made it a rule to give a dose which will cause a drop in the night blood sugar not greater than 10 mg. per hour from 10 p.m. to 8 a.m.

If the blood sugar is at the upper level of normal 170 mg. per cent at 10 p.m. and falls 10 mg. per hour until 8 a.m. it is then 70, which is getting toward a reaction level. It is undesirable to allow a fasting blood sugar to be this low because some day that patient will take more exercise than usual and have a morning reaction the next day. If the blood sugar is higher than 170 at 10 p.m. the patient with normal blood sugar level at night and fasting we cannot allow a fall greater than 10 mg. per hour. If the choice must be made between letting a patient have a high evening blood sugar and a low fasting one the high evening blood sugar is the better, because the early morning reactions are too upsetting.

In Table II, case 3, the patient was getting too large a dose, despite the fact that she showed sugar in the urine all afternoon; her blood sugar fell so fast that she had early morning reactions. Her dose of protamine zinc insulin was reduced by 10 units and she was given 10 units of the unmodified insulin at noon; on this dose she shows sugar in the late afternoon but not at other times, and she has no morning reactions. In case 4 the rate of fall was much too great; his dose was eventually reduced to 13 units a day of the protamine zinc insulin.

We have evolved the following working rule for transferring patients from unmodified insulin to protamine zinc insulin. Add the total number of units the patient is taking in 24 hours; if the total is under 40 add 5, thus, if the dose has been 10-5-10, making a total of 25, the initial dose of protamine zinc insulin would be 25 plus 5, that is, 30 units. In addition to this, 5 units of unmodified insulin is given for 5 days before breakfast. As soon as all tests in the 24 hours are sugar-free, reduce the dose of protamine zinc insulin 5 units a day; when the dose gets below 20 units reduce it 2 units a day. As soon as a positive test for sugar appears, cease reducing the dose. The 5 units of unmodified insulin can usually be discontinued after 5 days in these low-dose cases.

If the total units of unmodified insulin taken in 24 hours are more than 40 add 10 to the total for the beginning dose of protamine zinc insulin. For example, if the dose is 25-20-10-5, total 60, add 10, which gives the initial dose of protamine zinc insulin as 70; in addition give 10 units of the unmodified insulin before breakfast. Reduce the protamine zinc insulin 10 units a day as soon as all tests are sugar-free; the 10 units of unmodified insulin may or may not be discontinued, or they may be given at noon. When protamine zinc insulin has been given un-

Rules for Changing from Unmodified to Protamine Zinc Insulin

DOSE OF UNMODIFIED INSULIN 10-5-10. TOTAL 25.

Beginning dose of protamine zinc insulin would be 25 plus 5 = 30; also 5 units of unmodified insulin.

Reduce the protamine zinc insulin 5 units a day as soon as all four daily tests are sugar-free. Omit dose of unmodified insulin after five days. If dose of unmodified insulin totals less than 40 units 5 units are added to make up the protamine zinc insulin dose.

DOSE OF UNMODIFIED INSULIN 25-20-15. TOTAL 60.

Beginning dose of protamine zinc insulin would be 60 plus 10 = 70, also 10 units of unmodified insulin.

Reduce dose of protamine zinc insulin 10 units a day as soon as all tests are sugar-free. Unmodified insulin may or may not be reduced; this depends on fasting blood sugar which must not be lower than 70.

If total dose of unmodified insulin is more than 40 units 10 units are added to make the dose of protamine zinc insulin.

modified insulin should never be given later than noon; even with a positive test before supper the urine may be sugar-free before morning.

It takes about 5 days for the protamine zinc insulin to have its full effect, after that it can be reduced rapidly. In the instructions which come with the insulin put out by the Connaught Laboratories it is suggested that two-thirds of the former total daily requirement of unmodified insulin be given as the initial dose of protamine zinc insulin with one-third of the former daily requirement as unmodified insulin. We prefer the larger dose, even at the risk of an occasional morning reaction, because it shortens the patient's hospital stay, and the patient has fewer sugar-positive days.

When a fresh, untreated diabetic appears we clear him up as fast as possible with unmodified insulin; then, using the above rule, change to protamine zinc insulin. It takes about two weeks to do this. The patient is specially instructed to keep reducing his insulin if tests continue to be sugar-free at home. Children are so much more active at home than in hospital that the dose they are taking when discharged from the hospital bears little relation to their final dose, which is much lower.

Clinical and Laboratory Notes

RATIONAL TREATMENT OF THE APPARENTLY DROWNED

By Alexander Fisher

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It is not enough to resuscitate a man if he is to die a few days later from a secondary pneumonia. All life-saving stations should be provided with electric blankets for quickly warming the body, also electric pads, mattresses, hot water bottles, a pocket sparklet, carbon-dioxide-oxygen inhalator which can be carried in a doctor's small grip, a French venesection outfit, coramine, adrenalin for intracardiac therapy, needles, etc.

An ordinary blanket is too easily displaced by the efforts of artificial respiration. The electric blanket is seven feet long, and can be wrapped well around the victim and is not easily displaced. It is claimed that this blanket raises the temperature of the living body, so quickly, that free perspiration starts in 15 minutes. When the victim is taken from the water he is chilled through. No doubt the extreme cold has anæsthetized him to such a degree that respiration is suspended. Extreme shock is present. I cannot see how we can be successful in resuscitating these persons unless we quickly raise their body temperature. The resuscitation should be carried on near the water's edge, immediately after the victim has been rescued.

Thiel is of the opinion that the usual methods employed to remove water from the lungs in these cases are useless and may cause the loss of valuable time. After the nose and the throat have been cleaned, the respiratory passages should be cleared by means of Witzel's suspension of the head and by drawing out the tongue. Then artificial respiration should be started at once after the victim has been covered with the electric blanket.

Dr. C. J. Mijnlieff, Amsterdam, Secretary-General for the International Life Saving Society writes in *The Lancet* of July 20, 1935, that scientific investigations have led us to change our views of the requirements which a method of artificial respiration must meet. His investigation of the present methods of artificial respiration has led him to the opinion that a modified Silvester's method is superior to Schafer's method. This method he claims gives the best ventilation of the lungs. His modified Silvester's method of artificial respiration is described in *The Lancet* in detail.

There are two types of apparently drowned persons described, the common cyanotic type and the uncommon pallid type. In both types there is damming back of the blood in the splanchnic region of the abdomen. In the cyanotic type, the left side of the heart is emptied of blood, while the right side of the heart and the venæ cavæ and pulmonary artery are filled to the fullest extent. The portal system is overfilled. The aorta and the large blood vessels are empty. The spleen, liver, kidneys, and meninges are engorged with blood. In the pallid type, the arterial and the venous system are empty all the blood being in the portal system. In the cyanotic type death is due to damming of the blood in the splanchnic area. It is considered that artificial respiration should be supplemented by oxygen and carbon-dioxide inhalations and oxygen injections into the arteries and veins. It is claimed that venesection with the removal of 400 c.c. of blood from the cyanotic patient is urgently indicated, as it will relieve the right side of the heart. Intracardiac injections of adrenalin have also been recommended. The inhalation of a mixture of oxygen and carbon-dioxide 5 to 8 per cent is a very potent stimulant of respiration.

The Surf Life-Saving Association of Australia believe that rubbing and slapping of the palms of the hands and the soles of the feet should be discontinued, and that where assistance is available the treatment of shock should be begun immediately the patient is brought to shore.